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## TOWARD A QUANTITATIVE VIEW OF THE ENGRAM\*

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The qualitative nature of memory remains unknown, but common experience and laboratory observations attest to its quantitative character. Memories may be "strong" or "weak," as judged subjectively or as inferred from animal experiments. The typical experimental measure of a memory is the probability of emission of a learned behavioral response, the observable indicant of the memory. Each indicant is considered to reflect a corresponding memory trace in the brain, the so-called engram. The indicant is quantified, but the corresponding engram is not. This dichotomy adds a conceptual gap to the physiological gap that separates an engram from its indicant. There is a need for language to describe the engram in a quantitative sense, in order to link it more definitely with its measured indicant. It seems timely to introduce a quantitative unit of memory, even though such a unit must as yet be hypothetical, speculative, and tentative.

The proposed unit is defined as the minimal physical change in the nervous system that encodes one memory. The unit cannot be assigned physical dimensions until the nature of the engram is known; for the present, it may be thought of as a single facilitated neural pathway, or a single encoded macromolecule, or a single unit of whatever the engram is. The "strength" of a memory is a function of the number of units that encode the memory. In the limiting case, the "weakest" engram consists of one unit. The name proposed for the unit is the "mnemon" (mneme = memory; -on = suffix denoting a fundamental particle).<sup>1</sup> The potential usefulness of the mnemon concept is illustrated by its application to two current problems.

*Controversy about the Memory Consolidation Hypothesis.*—Long-term memory

involves read-in, storage, and read-out of information. The hypothesis of memory consolidation<sup>2</sup> offers a clue to the read-in process, by leading to the inference that the experimentally determined time-course of read-in bears some definite relationship to the kinetics of the *rate-determining* step of the underlying process of engram formation. The time-course is determined with retrograde amnesia experiments<sup>2-5</sup> by measuring the rise of the indicant as a function of time after a learning experience. The hypothesis is currently embarrassed by widely differing values for consolidation time, ranging from 10 to 900 sec in apparently comparable experiments.<sup>3-5</sup> Differences of this kind contribute to conflicting interpretations of what retrograde amnesia experiments measure.<sup>6</sup> The mnemon concept offers an alternative view that reduces the apparent conflict. The conceptualization employed is:



Pro-mnemons are visualized as the unstable units of short-term memory, with a half life on the order of 10–100 sec. Mnemons are assumed to be relatively stable, with a half life of  $10^7$  seconds (4 months) or more. The number of pro-mnemons produced during a learning experience is a function of the many variables that determine “learning strength.” The number of mnemons produced is a function of the number of pro-mnemons present, the available concentration of “consolidator,” and, in retrograde amnesia experiments, the time allowed for uninterrupted consolidation. Probit analysis<sup>7</sup> of three recent experiments<sup>3-5</sup> on retrograde amnesia after one-trial learning in rats reveals that the probability of indicant emission fits a normal distribution with the logarithm of the time allowed for consolidation.<sup>7</sup> The regression lines are described by the equation  $y = \alpha + \beta \log t$ , where  $y$  = probit of indicant,  $\alpha$  = constant for each experiment,  $\beta$  = slope constant, and  $t$  = time between learning trial and interruption by electroconvulsive shock (in sec). The slope constants shown in Table 1 are not significantly different ( $p = 0.05$ ), leading to the inference that the same rate-determining step was operating. The difference in consolidation half times is therefore inferred to be due to a smaller pulse of pro-mnemons in experiment 3 than in experiments 1 and 2. This view may be compared with the conventional view that the rates of consolidation vary widely, which implies different rate-determining steps of consolidation.

The pulse of pro-mnemons may be considered to reach a peak approximately one second after the learning experience. At that time,  $y = \alpha + \beta \log 1$ , and  $\alpha = y$ . If the mnemon concept is correct,  $\alpha$  values could be used to quantitate “learning

TABLE 1  
CONSOLIDATION TIMES (CT), CONSOLIDATION HALF TIMES ( $CT_{50}$ ),  $\alpha$  VALUES,  
AND SLOPE CONSTANTS ( $\beta$ )

Expt.	Reference	CT (sec)*	$CT_{50}$ (sec)	$\alpha$	$\beta^\dagger$
1	Chorover and Schiller <sup>2</sup>	10–30	6.6 (4.6–9.5)‡	3.3	2.1 (1.7–2.8)‡
2	Quartermain <i>et al.</i> (ref. 4)§	30–60	9.8 (6.9–14.3)	3.5	1.5 (1.2–2.1)
3	King <sup>5</sup>	300–900	1100 (500–2580)	0.6	1.5 (0.9–3.8)

\* Published lower and upper limits of retrograde amnesia. Each experiment employed: one-trial learning of a passive-avoidance response in rats; conditioning by foot-shock; interruption by electroconvulsive shock; at least 10 rats per group; and at least 4 trial-to-ECS intervals. A fourth experiment<sup>3</sup> met the foregoing criteria, but the data proved to be significantly heterogeneous by the chi-square test and are not included here.

†  $\beta$  is the slope constant in  $y = \alpha + \beta \log t$ . The weighted mean of  $\beta$  is 1.9.

‡ 19/20 confidence limits.

§ The 0.1-sec datum has been suppressed because of probable uncertainty in the time measurement.<sup>7</sup>

strength," in probits. On the other hand, a demonstration that  $\alpha$  is unrelated to "learning strength" could be used to invalidate the concept.

*Learning Curves and Forgetting Curves.*—In a sense, learning curves display the rise of an indicant of memory as a function of the number of learning trials. Forgetting curves<sup>8</sup> display the decay of the indicant with time. By the mnemon concept, both curves are end portions of a single curve. The curve has an intermediate plateau section due to the ceiling effect when the indicant is at its maximal value (ideally, a 100% response). The rise of the indicant during learning is considered to reflect the increase of mnemons with each learning trial and with time, and the plateau reflects the supramaximal level of mnemons. The forgetting curve begins when the mnemon level falls below that required for the maximal indicant level. Bahrick<sup>8</sup> has made a critical detailed analysis of the process of memory decay; his reasoning is applicable to the process of memory formation. He has applied to forgetting-curve data a *Z*-transformation which is essentially the probit transformation (*Z*-score + 5.00 = probits) and has arrived at an "ebb" unit to describe the course of forgetting. Ebbs are equal to probits, but the latter have the advantage of applicability to both the rise and fall of memory indicants.

*Summary.*—The concept of a hypothetical quantitative unit of long-term memory, the "mnemon," is proposed. Its utility is illustrated by applying the concept to descriptions of memory consolidation and of learning and forgetting curves.

*Note added in proof:* After submission of this article, Dr. J. Z. Young kindly allowed me to see his Croonian Lecture, *Proc. Roy. Soc. (London)*, Ser. B, 163, 285 (1965), before publication. He applies "mnemon" to an anatomical unit of memory, viz., a module comprising an activated classifying neuron and its closely associated cells. This specific application of "mnemon" is compatible with the general definition proposed in this article.

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## THEORY OF THE FLOW OF ACTION CURRENTS IN ISOLATED MYELINATED NERVE FIBERS, IX\*

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We continue the presentation of the theory of the isolated fiber.<sup>1</sup>

*Effect of Saponin upon the Resting Membrane Potential.*—According to reports in the literature,<sup>2, 3</sup> 2 per cent saponin in Ringer's does not depolarize the internodes of isolated fibers until, after long-lasting action (20-40 min), it causes disintegration of the myelin layer. However, when, instead of a condenser-coupled amplifier which cannot detect flows of demarcation current, a d.c.-coupled amplifier is used, it is found that 2 per cent saponin is an exceedingly powerful depolarizing agent; indeed, it is stronger than 114 mM potassium chloride. The depolarization by saponin begins almost instantaneously and increases progressively during a long period of time (no less than 40-60 min). The experiments illustrated by Figures 1-3 belong to a series of 12 in which perfectly consistent results were obtained, for which reason only two experiments will be discussed in which node  $N_1$  was placed in different positions. In all cases, at the end of the experiment microscopic examination (300 $\times$ ) failed to detect structural changes in the treated segment, which is in agreement with the fact that in fibers of desheathed nerves kept in 2 per cent saponin for 30 min the myelin layer is stained by osmic acid in apparently the same manner as in untreated nerves.

*Node  $N_1$  at the Center of the First Gap and Exposed  $N_2$  in the Distal Pool.*—The experiment illustrated by Figure 1 is exceptional, since it is the only one in which, with node  $N_1$  at the center of the first gap, an early downward peak did not appear when the amplifier was placed across the first gap (Fig. 1, 1). In all probability, the stimulation threshold in the central pool was higher than in all the other similar experiments. Nevertheless, the threshold still was low enough (cf. ref. 1b) to permit the creation of an active zone in the central pool when a zero-resistance shunt was placed across the first gap (Fig. 1, 2). That the stimulation threshold was relatively high in the central pool is also proved by the fact that with the amplifier in position IV, a deflection was recorded (Fig. 1, 3) having a small downward phase and a large second upward phase (refs. 1 c, e, h). In view of the rapid action of 20 mM xylocaine (Fig. 1, 4-8), it is clear that the active zone responsible for the second upward phase was located in the distal pool. The secondary action of the anesthetic, which also developed rapidly, depressed the state of the isolated fiber. For this reason, with the amplifier across the first gap, an active zone was not created in the central pool and only a trapezoidal action potential was recorded (Fig. 1, 9). With the amplifier across the second gap, in the presence of a zero-